Regulation of MAGI-1 expression and function in breast cancer

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Breast cancer (BC) is a heterogenous disease and based on molecular characteristics BC can be stratified in four main subtypes: luminal A, luminal B, HER2-enriched, basal-like and normal-like subtypes. MAGI-1 is a scaffolding protein that modulates cell-cell contacts and cell adhesion. MAGI-1 was suggested as a new potential tumor suppressor gene in the ER^+ BC subtype. Previous data showed that MAGI-1 is downregulated by prostaglandin E_2 (PGE_2) and upregulated by nonsteroidal anti-inflammatory drugs (NSAIDs) in colorectal cancer (CRC). Recently our lab showed that NSAIDs upregulates MAGI-1 in MCF-7 cells. These observations suggested that MAGI1 may be broadly down-regulated by inflammation.

The aim of this study is to investigate the regulation of MAGI-1 expression in BC cell lines in response to inflammatory cytokines. We exposed ER^+ MCF-7, $ER^+/HER2^+$ BT-474; triple-negative MDA-MB-231 cells and HCT116 CRC cell lines to the pro-inflammatory cytokines TGFβ, TNFα, IL1β, and IL6, PGE_2 and COX1/2 inhibitors for 6, 24 and 48 hours and monitored mRNA expression of MAGI-1, COX-2, ESR1 and ICAM-1 by RT-PCR. mRNA expression was also measured HUVEC. Western Blotting was performed to identify protein levels of MAGI-1, ESRα in the different cell lines. RT-PCR results showed an induction of ICAM-1 mRNA by TNFα and IL1β in all tested lines. Treatment with NSAIDs induced MAGI-1 expression, while treatment with cytokines did not reduce MAGI-1 mRNA expression. Treatment, with TNFα and IL1β induced mRNA expression of COX-2 in all cell lines. Taken together, these results demonstrate that NSAIDs promote MAGI-1 mRNA expression. Inflammatory cytokines, however, did not decrease MAGI-1 mRNA expression. Thus, we conclude that inflammation is likely not a main mechanism responsible of MAGI-1 downregulation in BC.

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